REMARKS

Claims 1-29 and 70-86 are pending in this application. Claims 1, 2, 4, and 15-29 have been amended. New claims 83-86 are added. Support for the new claims and amendments can be found throughout the specification and claims as filed.

Specification

The disclosure was objected to for containing embedded hyperlinks. Applicants have amended the specification to remove the hyperlinks.

Rejection of Claims 4-7 and 18-29 Under 35 U.S.C. §112, first paragraph

Claims 4-7 and 18-29 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description. In particular, the Examiner asserts that

> Applicant's amendments to the claims are not deemed sufficient to overcome the rejection of record because the specification has not specifically taught a representative genus of variants to represent the highly variant genus of peptides claimed. Specifically, the claims are still drawn to sequences that are not adequately defined or disclosed in the specification as filed.

The Examiner alleges that claims 4-7, drawn to MUC1-specific binding members comprising a CDR having conservatively substituted sequences of amino acids 99 to 110 of SEQ ID NO:3, are not adequately described by the specification as filed. Applicants respectfully traverse this rejection. Conservative amino acid substitutions, i.e., substitutions that replace one amino acid residue with another "of similar structure, charge, or hydrophobicity" (page 23, line 11) are well known in the art and often result in proteins with similar activity to the parent protein. Several representative species of MUC1-specific binding members with conservative substitutions of amino acids 99 to 110 of SEQ ID NO:3 are described in the application. See, e.g., SEQ ID NO:28, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:88, SEQ ID NO:93, SEQ ID NO:99, SEQ ID NO:104, and SEQ ID NO:106. Most of these species bind to MUC1 as well or better than the parent polypeptide having amino acids 99 to 110 of SEQ ID NO:3 (see Table 9, pages 56-57). Applicants submit that the species presented are sufficient to represent the genus

of MUC1-specific binding members having conservatively substituted sequences of amino acids 99 to 110 of SEQ ID NO:3, to show that applicants were in possession of the claimed binding members at the time of filing.

The Examiner further alleges that claims 18-29, drawn to MUC-1 specific binding members comprising an amino acid sequence that is 70%, 80%, 90%, 95%, 97%, or 99% or more homologous to any of the sequences of amino acids 97-110 of SEQ ID NO:3, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, and amino acids 99 to 110 of SEQ ID NO:3, is not adequately described by the specification as filed. Again, applicants respectfully traverse this rejection. As pointed out in previous replies, the homology is to peptides only about 14 amino acids in length. Thus, the claims set a clear limit on the number of amino acid substitutions, insertions, or deletions that can be made. For example, a sequence that is 70% or more homologous to SEQ ID NO:29 would have at most four amino acid substitutions. The specification presents several species of MUC1-specific binding members that are representative of the genus of MUC1-specific binding members comprising an amino acid sequence that is 70% or more homologous to the above sequences (see Table 9, pages 56-57). All of these representative species have the claimed function of binding MUC1, and most bind as well as or better than the parent antibody PH1. Further, a MUC1-specific binding member that has SEQ ID NO:95, which has four amino acid substitutions compared to SEQ ID NO:29 or SEQ ID NO:30, binds strongly to MUC1 (Table 9). Thus, there is sufficient description of a representative number of species to support the claimed antibodies.

The Examiner alleges that these claims are "analogous" to Example 13 of the Revised Interim Written Description Guidelines. Applicants respectfully disagree for several reasons. In Example 13, only one representative species of the claimed genus is disclosed, whereas applicants disclose several representative species. Also, no function of the disclosed sequence is provided in Example 13. *Applicants not only disclose a function of the species, but require that the claimed species have such function.* Furthermore, the specification and claim of Example 13 place no limit on the type or number of amino acid substitutions, deletions, or insertions that may be made to the disclose sequence. The instant specification and claims require either MUC1-

specific binding members with conservative substitutions of a portion of the polypeptide or 70% or more homology within a short stretch of amino acids. Lastly, the instant specification provides specific guidance as to the type of substitutions that can be made, in variant sequences SEQ ID NOs:28-32 and SEQ ID NOs:73-109. Therefore, unlike the case of Example 13, applicants clearly disclose a representative number of species to describe the claimed genera.

In fact, applicants argue that the description provided for the claims at issue is more similar to, and even better than, that presented in Example 14 of the Revised Interim Written Description Guidelines. In this example, the claim is drawn to a genus of proteins comprising variants of an amino acid sequence that are at least 95% identical to the sequence and catalyze a reaction. The disclosure of one amino acid sequence and a function was determined to be sufficient to claim the genus of proteins that are 95% identical to the disclosed sequence and had the same function. In the instant matter, applicants have disclosed 41 representative MUC1-specific binding members that bind MUC1 (SEQ ID NOs:29-32 and SEQ ID NOs:73-109). Applicants argue that this is a more than sufficient number to describe the claimed genera with 70% or greater homology within a short stretch of amino acids.

The Examiner has stated that "Wu X *et al* (Clin. Immunol. Immunopathol. 1998; 87:184-192) teach an antibody that comprises a substitutions at position 99 and falls within the scope of the claimed MUC-1 binding protein and yet it is an antibody that is specific for myosin." Although the antibody of Wu et al. teaches an antibody that comprises an amino acid sequence identical to amino acids 99-110 of SEQ ID NO:1, this is not relevant to the claims at issue, which specify amino acids 99-110 of SEQ ID NO:3. Amino acids 99-110 of SEQ ID NO:1 are part of the antibody framework sequence, whereas amino acids 99-110 of SEQ ID NO:3 are the CDR3 sequence. Thus, Wu et al. is irrelevant for determining if there is sufficient description for the claimed binding members.

In view of the preceding arguments, applicants respectfully request reconsideration and withdrawal of the rejection of claims 4-7 and 18-29 under 35 U.S.C. §112, first paragraph.

Rejection of Claims 1, 2, 4-14, and 75-79 Under 35 U.S.C. §112, second paragraph

Claims 1, 2, 4-14, and 75-79 are rejected under 34 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants disagree with this rejection, but have amended claims 1 and 4 to recite specific framework regions, solely to further prosecution. Applicants request withdrawal of this rejection.

Rejection of Claims 24-29, 80, and 81 Under 35 U.S.C. §101

Claims 24-29, 80, and 81 are rejected as allegedly not distinguishing the claimed subject matter over naturally existing proteins. Applicants have amended the claims to recite that the polypeptide molecules are "isolated." Applicants request withdrawal of this rejection.

Rejection of Claims 1, 2, 4-29, and 70-81 Under 35 U.S.C. §112, first paragraph

Claims 1, 2, 4-29, and 70-81 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabling for a MUC1-specific binding member comprising fewer than three CDR regions in any and all generic framework regions or germline framework.

Based on an evaluation of the factors outlined by the court in *In re* Wands, the Examiner argued that it would require undue experimentation for one of skill in the art to perform the methods of the claimed invention.

The Examiner states that, "The claims read broadly on a MUC-1 specific binding member that consists of a single CDR regions from SEQ ID Nos.:1 and or 3 wherein the member can be peptides, antibodies or antibody fragments." Applicants have amended independent claim 1 to recite, "An isolated MUC1-specific binding member comprising a light chain variable domain, or portion thereof, and a heavy chain variable domain, or portion thereof...." Applicants have amended independent claim 4 to recite, "An isolated MUC1-specific binding member comprising: a heavy chain variable region, or portion thereof; a light chain variable region, or portion thereof; and...." Applicants have amended independent claims 15-18 to each recite, "A MUC1-specific antibody or antigen-binding fragment thereof...."

The Examiner states that, "Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al" (Rudikoff). Although Rudikoff does teach that a single amino acid substitution in the CDR of an antibody resulted in the loss of antigen-binding function, Rudikoff teaches that this is not typical.

> [I]t is clear that all such substitutions need not and probably do not affect antigen binding. For example, the heavy chain from the *P*-Cho-binding myeloma protein M167 differs from that of S107 at 13 positions (8 in hypervariable regions including a size difference) and yet has an association constant for hapten only slightly lower than S107. We have previously shown that, among anti-1,6-galactan-binding myeloma proteins, as many as eight or nine substitutions may occur in hypervariable regions with no significant effect on hapten affinity or specificity. (p.1982)

Rudikoff further concludes that "small numbers of substitutions in antibodies, such as those presumably introduced by somatic mutation, may in *some* situations be effective in altering antigen-binding specificity" (abstract, author's emphasis). Therefore, it is clear that Rudikoff does not teach that minor changes in the variable regions of antibodies are likely to affect antigen-binding function, but rather that, except in rare instances, minor changes are likely to be tolerated.

The Examiner asserts that significant study would be required to identify residues that are required for binding specificity of the MUC1-binding proteins. As described above, several amino acid substitutions of the MUC1-binding proteins have been identified that either retain or improve MUC1 binding activity. These identified amino acid substitutions provide guidance to predict those amino acid residues that may be substituted or conservatively substituted. Furthermore, the instant application describes a process of affinity maturation by mutagenizing the MUC1-binding proteins and selecting for mutagenized proteins that retain or improve MUC1 binding activity. This technique can be used with a high expectation of success to identify substituted MUC1-binding proteins with MUC1 binding activity.

The Examiner also alleges that the specification lacks guidance for MUC1-binding proteins in different framework sequences. However, framework swapping of antibodies is a common practice, and the specification provides specific guidance in this respect, for example at

page 11, line 19, to page 12, line 6. The specification provides, at page 11, techniques that involve

> introducing DNA comprising a nucleotide sequence(s), which, for example, encodes the immunoglobulin variable regions of the variable light (V_L) and/or variable heavy (V_H) immunoglobulin chains of a Fab or other MUC1-specific antibody, or which encodes portions of the V_L and/or V_H, such as one or more of the complementarity determining regions (CDRs), in frame with another DNA sequence, such as a nucleotide sequence encoding an immunoglobulin constant region or constant region and framework (FR) regions of a different immunoglobulin (see, e.g., EP-A-184187, GB 2188638A, EP-A-239400).

The combination of guidance in the specification and knowledge in the art is sufficient to allow the production and use of MUC1-binding protein with different framework regions.

Thus based on the scope of the claims, the relative predictability of antibody binding, the quantity of experimentation required, the numerous working examples, the ample guidance in the specification, and the high skill level in the art (which is admitted by the Examiner), applicants submit that it would not require undue experimentation for one of skill in the art to make and use the claimed antibodies and binding members. Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

Applicants respectfully request withdrawal of all rejections and the allowance of the above-referenced application.

Enclosed is $225 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 10280-075002.

Respectfully submitted,

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